Lung Cancer Screening

Patrick Nana-Sinkam, MD, FCCP
Associate Professor of Medicine
Co-Director Research Programs
Division of Pulmonary, Allergy,
Critical Care & Sleep Medicine
The Ohio State University Wexner Medical Center

What is new in lung cancer?

- New Staging system
- Goal of simultaneous diagnosis and staging
- Advantages of EBUS/EUS
- PET scan caveats
- Importance of EGFR/ALK status in treatment decisions
- Screening

Learning Objectives

- Review the epidemiology of lung cancer
- Historical perspective on lung cancer screening
- National Lung Screening Trial
- Current guidelines for lung cancer screening

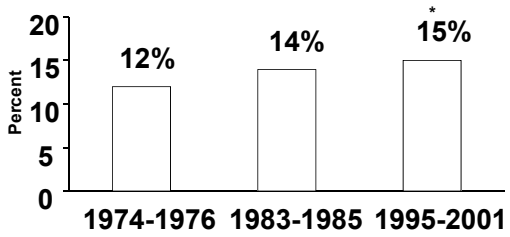
Lung Cancer in the United States

New Cases	Rank	Deaths	Rank
239,320	1	161,250	1*

*More deaths than prostate, breast and colon cancer combined; 85% of lung cancer is NSCLC

Jemal A et al. CA Cancer J Clin. 2011

5-Year Survival for Lung Cancer Over the Past 25 Years



*P<0.05 vs 1974-1976

Jemal A et al. *CA Cancer J Clin.* 2006;56:106.

Risk Factors for NSCLC

- Smoking (85% of cases)
- Occupational carcinogens
  - Asbestos
  - Radon
  - Nickel
- Nutrition/Diet
- Genetic factors
- 2nd Hand Smoke (~5%)

Lung cancer is a global problem

Global Scan 2008

Challenges in Lung Cancer Diagnosis and Treatment

- How do we screen for lung cancer?
- How do we identify "early disease"?
- Are we staging patients correctly?
- Identifying new therapeutic targets
- Further characterizing the molecular heterogeneity in lung cancer
- Clinically relevant biomarkers (sputum, blood, CT, tumor?)
- Is lung cancer in non-smokers a different disease?

Case

- 60 year old male presents to your clinic to enquire about being "screened" for lung cancer
- 60 pack year smoker
- HTN, DM
- Fam hx: CAD
- Exam: nonfocal
- How would you advise this patient?

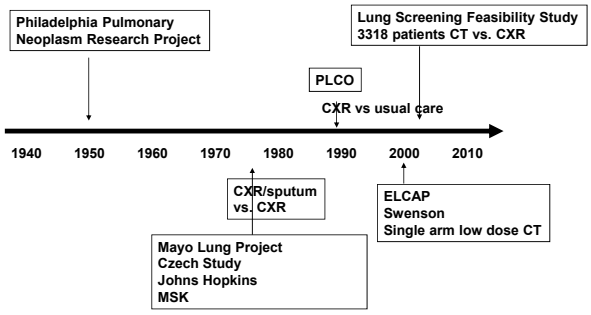
Keys to Lung Cancer Screening?

- Sensitive
- High incidence and prevalence
- Diagnose early treatable disease
- Decrease number of patients with late disease
- Cost effective
- Decrease mortality
- Lack of overdiagnosis
- Minimal morbidity

Rationale for Lung Cancer Screening

- Smoking cessation helps, but residual risk remains
  - Quit at age 50 risk by age 75 is 6%
- Improved *survival* with early stage disease
  - 5-Yr Survival all comers: 15%
  - Resected clinical Stage I: 92% per I-ELCAP;
    75 % SEER
- Why not start screening high-risk individuals now?

Historical Perspective on Lung Cancer Screening



Mayo Lung Cancer Screening Project

9211 Study Participants

Screened Group CXR & pooled sputum q 4 months	Standard care recommendation at study entry
Lung Cancers=206 Stage I & II (resected) 83 (40%) Late-stage (unresected) 123 (60%)	Lung Cancers=160 Stage I & II (resected) 41 (25%) Late-stage (unresected) 119 (75%)

- Between 1971 and 1983
- Screened: every 4 months for 6 years
- Control of CXR and sputum annually
- Survival: 40% in screened and 15% in control
- No difference in mortality

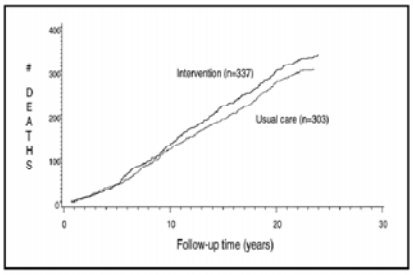
Marcus, JNCI, 2000

International Early Lung Cancer Action Project

- Based on ELCAP
- Prospective, international, multi-institutional study
- 31,567 patients at high risk for lung cancer screened
- Criteria for enrollment varied by institution
- 27,456 annual screens

I-ELCAP Investigators. NEJM 2006; 355:1763-1771.

Mayo Lung Project Lung Cancer Mortality



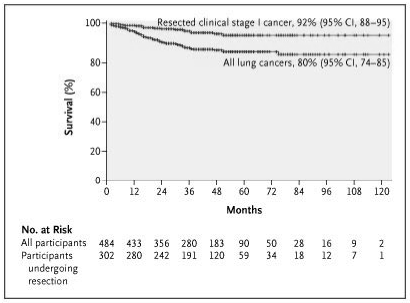
- Extended follow-up through 1996 using part national death index
- Median follow-up of 20.5 years
- No difference in mortality (4.4 deaths /1000 versus 3.9/1000)

Marcus, JNCI 2000

ELCAP

- Low-dose CT per ELCAP protocol
- Diagnostic work-up recommended but decision as to how to proceed left to individual and their physician
- Total lung cancers 484 out of 535 biopsies
  - 412 (85%) Clinical Stage I
  - Benign diagnoses: 43; Lymphoma or metastases from other cancer 13
  - 90.5% positivity rate

I-ELCAP Investigators. NEJM 2006; 355:1763-1771.



I-ELCAP Investigators. NEJM 2006; 355:1763-1771.

Sounds Good Right? Maybe not

- No comparison group
- Lead time bias
- Survival versus mortality
- Inconsistencies in lung cancer deaths
- No comment as to how many biopsies done outside protocol
- What was the course of those with positive screening but no biopsy?
- 10 year survival estimated to be 88% but median follow-up was 40 months

…however, the debate continues

Dr. Henschke's estimate that CT screening could reduce deaths by 80 % is "an outrageous and implausible claim." But … "it really got people to pay attention."

Dr. Peter Bach, NYT Tuesday, October 31, 2006

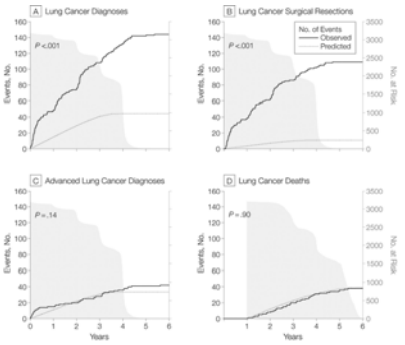
Longitudinal analysis of 3246 asymptomatic current or former smokers

Screening started in 1998

Annual CT scans median followup is 3.9 years

144 diagnoses among screened compared to 44.5 expected

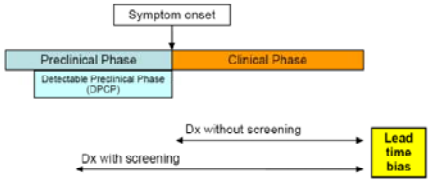
Increased diagnoses and resections



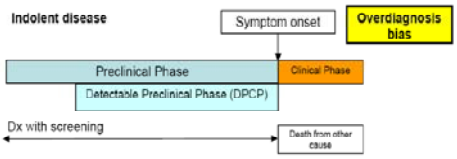
Bach, P. B. et al. JAMA 2007;297:953-961.

JAMA

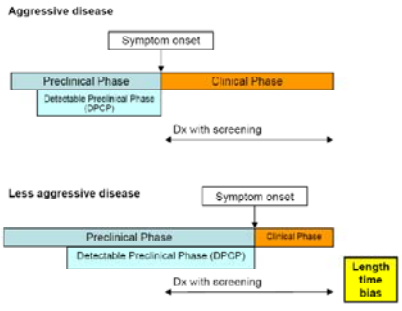
Lead Time Bias



Overdiagnosis



Length Time Bias



Lessons From CT Observational Trials

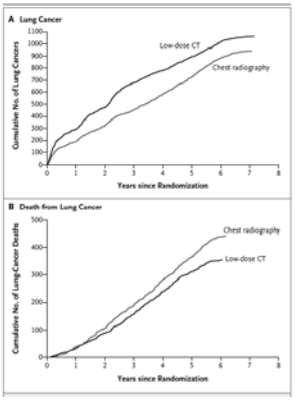
- **Detected prevalence rate: 0.40 – 2.7%**
  - **Age is strong risk factor (> 60 years)**
  - **Pack year smoking history**
- ***Nodule* detection rate variable on CT: 5.1% - 51.4%**
  - **Function of [a] definition of "nodule" and [b] CT slice thickness**
  - **Benign nodules = majority of detected nodules: ~90%)**
- **CT results in *higher* lung cancer detection than CXR**
  - **≥ 3-fold higher detection rate vs CXR; excess cancers early stage**
  - **2-3 fold selective oversampling of adenocarcinoma**
  - **Stage shift *not* yet been shown**

NLST

- Randomized CXR versus low-dose helical CT scan
- Initially screening followed by annual for two years
- 53,454 participants
- Ages 55-74
- Heavy smoker or former smoker (30 pack years)
- Asymptomatic
- No prior cancer
- Powered to detect 20% reduction in mortality

NLST (2002-2009)

- Initial screening 39% positive rate in low-dose CT and 16.0% in CXR
- 96.4% (CT) and 94.5% (CXR) false positive rate
- 1600 (CT) and 941(CXR) lung cancers
- 20% reduction in lung cancer related mortality
- 6.7% reduction in all cause mortality
- 90% Caucasian, 4.5% AA, 1.8% Latino



NEJM, 2011

Patient Demographics

Category	CT #	CT %	CXR #	CXR %	Total #	Total %
GENDER						
Male	15776	59.0%	15769	59.0%	31545	59.0%
Female	10951	41.0%	10968	41.0%	21919	41.0%
EDUCATION						
HS or Less	7913	29.7%	8047	30.2%	15960	29.9%
More than HS	18212	68.2%	18053	67.5%	36265	67.8%
SMOKING						
Current	12884	48.2%	12921	48.3%	25805	48.3%
Former	13837	51.8%	13805	51.6%	27642	51.7%

Radiology, 2011

N = 53,464

NLST Caveats

Important caveats (positives)

- Prospective randomized nature of study
- 6.9% reduction in all cause mortality
- No universal protocol for follow-up of positive CT scan so likely to be reproducible in community

Important caveats (negatives)

- Reduction in deaths in a target group (ages 55-74) so extrapolation not possible
- Small number of lung cancer deaths (LDCT 354 vs. 442 CXR)
- Cost analysis
- High false positive rate (96-97%)

NELSON

NELSON
Nederlands-Leuvens Longkanker Screenings Onderzoek

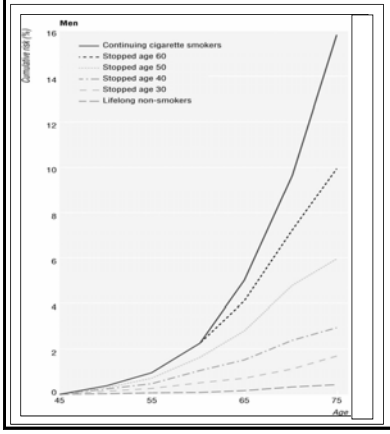
- Launched in 2003
- 16,000 patients
- Screening by MDCT versus no screening
- Years 1, 2 and 4
- Volumetric nodule assessment
- Powered to detect mortality reduction of 20%

Screening: public perspective

Characteristics	Never smokers	Former smokers	Current smokers	All subjects
	(n = 925)	(n = 517)	(n = 559)	(n = 2001)
Belief that he/she is at risk for lung cancer (%)				
Yes	2.8	7.7	23.1	
No	90.8	77.4	36.2	
Belief that early detection of lung cancer results in a good chance of surviving (%)	**58.8**	**54.0**	**48.7**	
Willingness to consider screening for lung cancer (%)	**87.6**	**86.1**	**71.7**	**82.8**
Willing to have surgery for lung cancer (%)	**69.2**	**62.5**	**50.5**	**62.2**

Silvestri GA, et al., Thorax, 2007

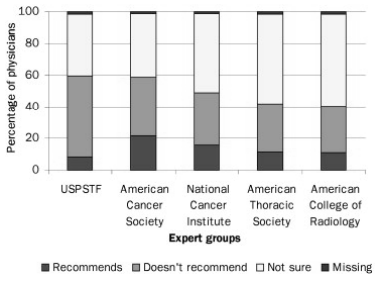
Smoking Cessation is Essential



Effects of stopping smoking at various ages on the cumulative risk (%) of death from lung cancer up to age 75, at death rates for men in UK in 1990. Nonsmoker rates were taken from US prospective study of mortality

Peto R, BMJ, 2000

Screening: physicians' perspective



N=962

Klabunde, C., American Journal of Preventive Medicine, 2010

Caveats to Lung Cancer Screening

- High false positive rates
- Cost analyses have yet to be completed
- Unclear how patients should be screened beyond 3 years of annual screening
- ASCO, ACCP and NCCN all now recommend screening for lung cancer in select patients
- Smoking cessation remains the most important intervention in these patients

Biomarkers for screening on the Horizon

- Exhaled breath condensate
- Circulating tumor cells
- Molecular staging
- Autofluorescence bronchoscopy

Ohio State Lung Cancer Screening

- Started May 2012
- Patient screened through James line 614 293-5066
- Inclusion criteria
  - 55-74 years of age
  - 30 pack smoker (current) or quit within 15 years
- Location: Martha Morehouse, every other Monday 4-6pm
- Cost 99.00
- CT conducted, interpreted and reviewed with patient during the visit
- Requires 3 annual CT scans
- Opportunity for Tobacco dependence clinic, General Pulmonary referral
- Expedited evaluation of pulmonary nodules if detected

Case

- 60 year old male presents to your clinic to enquire about being "screened" for lung cancer
- 60 pack year smoker
- HTN, DM
- Fam hx: CAD
- Exam: nonfocal
- How would you advise this patient?

Lung Cancer Screening

Efe Ozkan, MD
Assistant Professor
Section of Thoracic Imaging
Department of Radiology
The Ohio State University Wexner Medical Center

Why Lung Cancer Screening ?

- Prognosis depends on stage at diagnosis

Stage	5-year Survival Rate
IA	50%
IB	43%
IIA	36%
IIB	25%
IIIA	19%
IIIB	7%
IV	2%

J Thorac Oncol, 2007;2(8):706-14

Objectives

- Radiologic screening tests
- Radiologic screening trials
- Pulmonary nodule work-up
- Screening challenges

Ideal Screening Test

- Detect asymptomatic cancers
- Reduce lung cancer specific mortality rate

Ideal Screening Test

- Reasonable sensitivity, specificity, accessibility, cost and associated risks

NEJM 2000;343:1627-33

Screening Trials

- PLCO Trial
- I-ELCAP
- NLST

Which Radiologic Screening Test ?

- Chest X-Ray (CXR)
- Computed Tomography (CT)

PLCO Trial

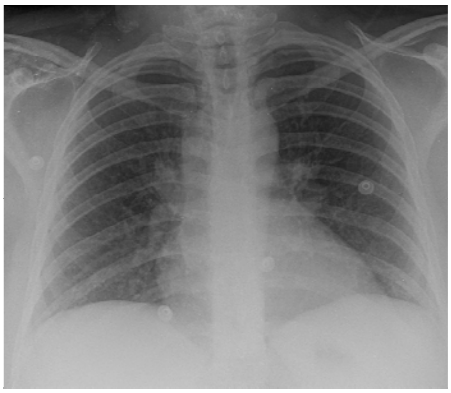
- The Prostate, Lung, Colorectal and Ovarian Trial
- Over 154,000 asymptomatic people
- PA CXR annualy for 4 yrs vs usual care – no screening

JAMA 2011;3406:1865-3

PLCO Trial

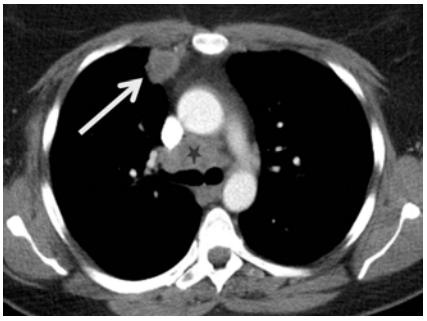
- Similar mortality rates between the two groups
- Annual screening with CXR does not reduce lung cancer mortality

JAMA 2011;3406:1865-3



Screening with CXR

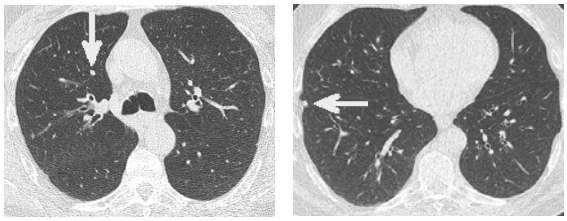
- Difficult to detect the early stage cancers with chest radiographs



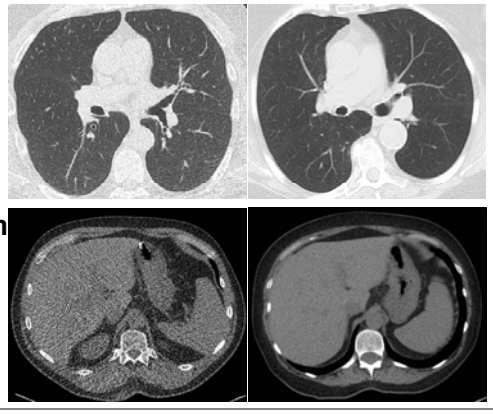
Screening with CT

- Multi-detector helical CT – Low dose
  - ✓ Entire chest in a single breath
  - ✓ Thin slice thickness
  - ✓ Detect smaller nodules
  - ✓ Free of partial volume effect

Low-Dose Chest CT



Low-Dose vs Routine Chest CT



1.5 mSv

I-ELCAP

- International Early Lung Cancer Action Program
- Over 31,000 asymptomatic people
- Low-dose CT between 1993-2005

NEJM 2006;355:1763-71

I-ELCAP

- Diagnosis of lung ca in 484 participant
- 412 (85%) had stage I lung ca
- 10-yr survival rate of 88%

NEJM 2006;355:1763-71

NLST Eligibility

- Age 55-74 years
- Current or former > 30 pack/yr smoking history
- If former smokers, quit in last 15 yrs

NEJM 2011;365:395-409

NLST

- National Lung Cancer Screening Trial
- Prospecive randomized controlled trial
- 33 sites in US
- Over 53,000 participants
- Annual screening for 3 consecutive yrs with Low-dose chest CT or CXR

NEJM 2011;365:395-409

NLST

- In November 2010, NLST was discontinued early because:

  Compared with CXR, CT reduced
  Lung cancer mortality by 20%
  All-cause mortality by 7%

NEJM 2011;365:395-409

NLST Lung Ca Mortality

CT Arm	CXR Arm
✓ 26,722 patients	✓ 26,732 patients
✓ 1060 lung ca	✓ 941 lung ca
✓ 365 deaths	✓ 443 deaths

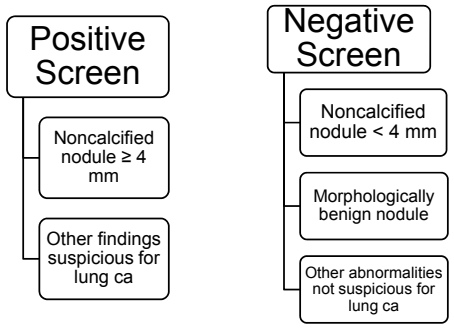
Relative reduction of 20% by CT

NEJM 2011;365:395-409

Pulmonary Nodule Work-Up

- Definitive benign features
- Suspicion of malignancy
- Fleischner Society recommendations
- Follow-up, PET/CT, biopsy, surgery

NLST Interpretation



NEJM 2011;365:395-409

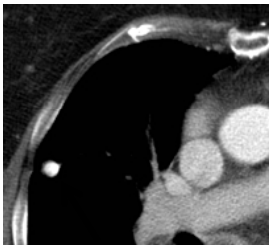
Benign Calcifications

- Prior infection (tb, histo)
  - ✓ Diffuse
  - ✓ Central
  - ✓ Contentric
- Hamartoma
  - ✓ Popcorn

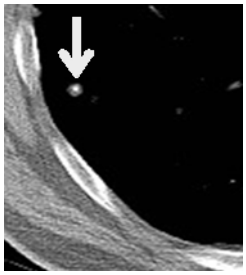
Pulmonary Nodule

Pulmonary Nodule

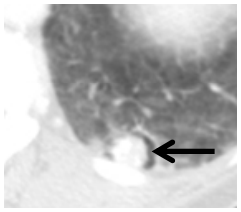
Diffuse Calcification=Benign



Central Calcification=Benign

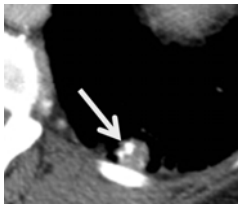


Pulmonary Nodule



Pulmonary Nodule

Popcorn Calcification=Benign (Hamartoma)

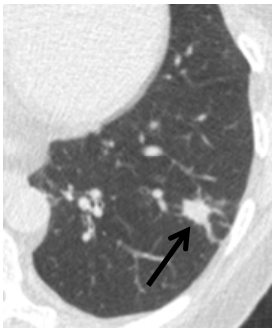


Intranodular Fat =Benign (Hamartoma)

Spiculated-Irregular-Lobulated Margin

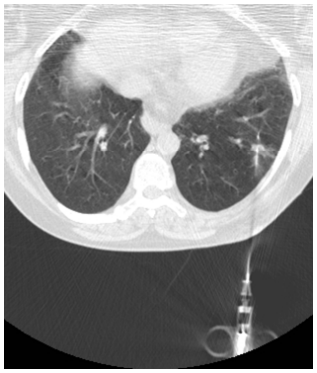
- Typically associated with malignancy
- Occasionaly infection/inflammation

Spiculated-Irregular Margin

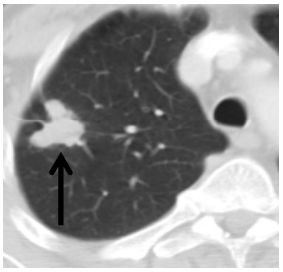


Spiculated-Irregular Margin

Biopsy



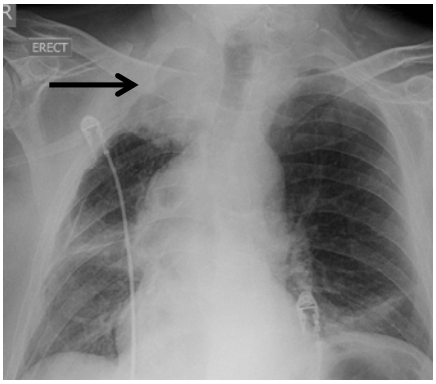
Lobulated Margin



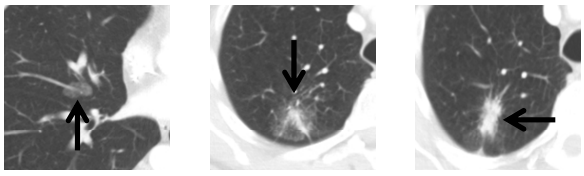
Density

- Ground glass opacity (GGO)
- Mixed solid / GGO
- Solid

Untreated-Lost to Follow-up



Density



GGO Mixed solid/GGO Solid

Adenocarcinoma in situ → Invasive adenocarcinoma

Size

- **Nodule : <3cm, benign or malignant**
- **Mass: >3cm, often malignant**

Radiology 2005;235:259-65

Growth

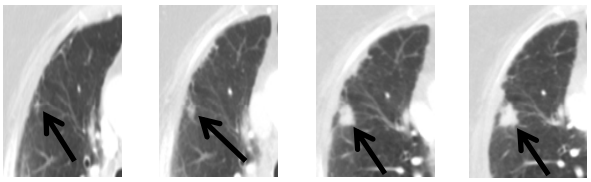
- **Doubling time (DT)**
- **Malignancy DT: 30-450 days**
- **Benign DT: <30 - >450 days**
- **Infectious/inflammatory: <20 days**

Size

Size	Total	Malignancy
< 4 mm	2038	0%
4-7 mm	1034	1%
8-20 mm	268	15%
> 20 mm	16	75%

Radiology 2005;235:259-65

Growth



4/2011 **1/2012** **7/2012** **10/2012**

Fleischner Society Recommendations

Nodule Size	Low-Risk	High-Risk
≤4 mm	No follow-up	12 mos
> 4–6 mm	12 mos	6-12 mos 18-24 mos
> 6-8 mm	6-12 mos 18-24 mos	3-6 mos 9-12 mos 24 mos
> 8 mm	3 mos 9 mos 24 mos	3 mos 9 mos 24 mos PET,biopsy,surgery

Radiology 2005;237:395-400

Fleischner Society Recommendations

- **DO NOT APPLY TO:**

✓ **Patients with known or suspected cancer**

✓ **Young patients < 35 yo**

✓ **Patients with unexplained fever**

Fleischner Society Recommendations

- **LOW RISK: minimal or absent hx of smoking or other known risk factors**
- **HIGH RISK: hx of smoking or other known risk factors**
- **KNOWN RISK FACTORS: hx of lung ca in 1st degree relative, exposure to asbestos, radon and uranium**

Screening Challenges

- **False-positive nodules: Most nodules are benign**
- **Cost effectiveness: Unknown**
- **Radiation exposure**

Radiation Exposure

- Background radiation: 3 mSv/yr
- Routine chest CT: 8 mSv
- Low dose chest CT: 1.5 mSv

Radiation Risk

- Lung cancer risk:
  50 yo F smoker: 16.9%
  50 yo M smoker: 15.8%
- Baseline screening low-dose chest CT:
  Fairly low risk for radiation induced lung cancer: < 0.06%

Radiology 2004;321:440-5

Radiation Risk

- Radiation-induced lung cancer risk
- Very low, but not negligible
- Estimates extrapolated from unrelated radiation exposures

Who should be screened ?

- No guidelines from US Preventive Services Task Force yet
- NCCN, ALA, ACCP/ASCO published recommendations

Who should be screened ?

- **NLST cohort is the only group with true evidence of benefit:**

✓ **Age 55-74 years**

✓ **Current or former > 30 pack/yr smoking history**

✓ **If former smokers, quit in last 15 yrs**

Where ?

- **In comprehensive care centers with diagnostic and treatment capabilities similar to those in the NLST**